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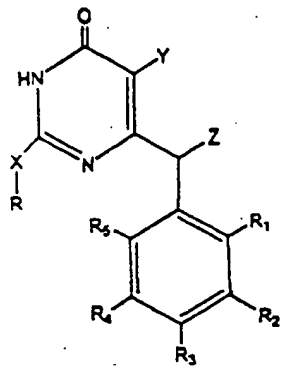
(54) Title: SUBSTITUTED 6-BENZYL-4-OXOPYRIMIDINES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract

The invention concerns novel substituted 6-benzyl-4-oxopyrimidines of general formula (A). These compounds inhibit reverse transcriptase encoded by human immunodeficiency virus (HIV) or pharmaceutically acceptable salts thereof, and find their application in the prevention and treatment of HIV infection and the treatment of the resulting acquired immune deficiency syndrome (AIDS). Pharmaceutical compositions containing the compounds and a method of use of the present compounds and other agents for the treatment of AIDS and viral infection by HIV are also envisaged.



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SUBSTITUTED 6-BENZYL-4-OXOPYRIMIDINES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention is concerned with compounds which inhibit the reverse transcriptase encoded by human immunodeficiency virus (HIV) or pharmaceutically acceptable salts thereof and are of value in the prevention of infection by HIV, the treatment of infection by HIV and the treatment of the resulting acquired immune deficiency syndrome (AIDS). It also relates to pharmaceutical compositions containing the compounds and to a method of use of the present compounds and other agents for the treatment of AIDS arid viral infection by HIV.

BACKGROUND OF THE INVENTION

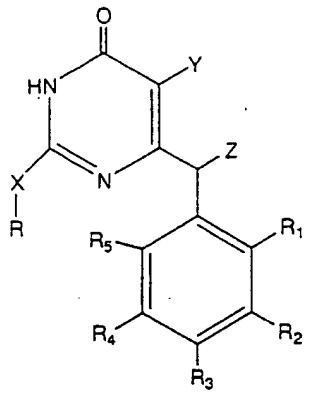
A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system.

Currently available drugs for AIDS therapy are divided into two groups: those that prevent infection of target cells [nucleoside (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs)], and those that prevent HIV-1-infected cells from yielding infectious viruses (protease inhibitors). Monotherapy with antiretroviral agents has shown limited effects, very likely due to the interplay of phenomena such as: high viral loads and multiplication rates of HIV, incomplete inhibition of viral replication and emergence of drug resistant mutants. For this reason, combination therapies with two or more drugs have been proposed for a more effective treatment of AIDS. Potent suppression of HIV replication over prolonged periods has been accomplished with regimens including reverse transcriptase and protease inhibitors, although on stopping therapies viraemia has rapidly reappeared. In the attempt to obtain better results, research is now focused on exploiting new targets and enhancing the activity of "old" drugs. Among the latter, NNRTs possibly endowed with better pharmacokinetic profiles, capability to inhibit clinically relevant mutants and, hopefully, to minimize HIV multiplication are being pursued.

Compounds of the present invention are dihydro-alkyloxy-benzyl-oxopyrimidines (DABOs) which potently inhibit HIV multiplication targeting reverse transcriptase without bioactivation.

BRIEF DESCRIPTION OF THE INVENTION

Novel compounds of formula A:



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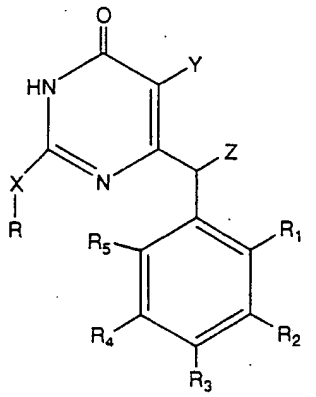
as herein defined, are disclosed. These compounds are useful in the inhibition of HIV reverse transcriptase, the prevention of infection by HIV, the treatment of infection by HIV and in the treatment of AIDS, either as compounds, pharmaceutically acceptable salts (when appropriate), pharmaceutical composition ingredients, whether or not in combination with other antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. Methods of treating AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV are also disclosed.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

This invention is concerned with the compounds of formula A described below, combinations thereof, or pharmaceutically acceptable salts thereof, in the inhibition of HIV reverse transcriptase, the prevention or treatment of infection by HIV and in the treatment of

the resulting acquired immune deficiency syndrome (AIDS). The compounds of this invention include those with structural formula A:



(A)

wherein:

X is -O, -CH_2, -CHK (wherein K is -H, -C_{1-4} alkyl, -C_{3-6}Cycloalkyl), -S, -NK (wherein K is -H, -Cl_{1-4}alkyl, -C_{3-6}cycloalkyl), -aryl, -arylalkyl;

R is -H, -C_{1-4}alkyl (containing one or more of heteroatoms like 0, S, N), -C_{3-6} cycloalkyl (containing one or more of heteroatoms like 0, S, N), -aryl, -arylakl, heterocycle;

Y is -H, -C_{1-4}alkyl, -C_{3-6}cycloalkyl;

Z is -H, -C_{1-4}alkyl, -C_{3-6}cycloalkyl;

R_1 is -H, -C_{1-4}alkyl, -halogen, -NO_2, -OW (wherein W is -H, -CH_3, aryl), -SW (wherein W is -H, -CH_3, -aryl);

R_2 is -H, -C_{1-4}alkyl, -halogen, -NO_2, (wherein W is -H, -CH_3, -aryl); -SW (wherein W is –H, -CH_3, -aryl);

R_3 is -H, -C_{1-4}alkyl, -halogen, -NO_2, -OW (wherein W is -H, -CH_3, -aryl); -SW (wherein W is –H, -CH_3, -aryl)

R_4 is -H, -C_{1-4}alkyl, -halogen, -NO_2, -OW (wherein W is -H, -CH_3, -aryl); -SW (wherein W is –H, -CH_3,-aryl)

R_5 is -H, -C_{1-4}alkyl, -halogen, -NO_2, -OW (wherein W is –H, -CH_3, -aryl), -SW (wherein W is -H, -CH3, -aryl);

- pharmaceutically acceptable salts or soluble derivatives thereof;
- preparation process of derivatives thereof;

- a method of preventing infection of HIV, or of treating infection by HIV or of treating AIDS, comprising administering to a mammal an effective amount of compounds claimed;
- a pharmaceutical composition useful for inhibiting HIV reverse transcriptase, comprising an effective amount of compounds claimed, and a pharmaceutically acceptable carrier;
- a pharmaceutical composition useful for preventing or treating infection of HIV or for treating AIDS, comprising an effective amount of compounds claimed, and a pharmaceutically acceptable carrier.

The most preferred compounds of this invention are those of table 1.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, individual diastereomers, or enantiomers, with all isomeric forms being included in the present invention.

When any variable occurs more than one time in any constituent or in formula A of this invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein except where noted, "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "Halogen" or "Hal" as used herein, means fluoro, chloro, bromo and iodo.

As used herein, with exceptions as noted, "aryl" is intended to mean any stable monocyclic, bicyclic or tricyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, biphenyl.

The term heterocycle or heterocyclic, as used herein except where noted represents a stable 5- to 7-membered monocyclic or stable 8- to 11 -membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, 0 and S; and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure.

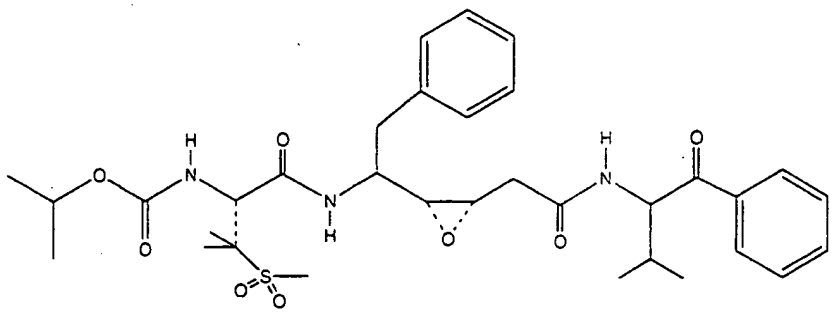
The pharmaceutically-acceptable salts of the novel compounds of this invention that are capable of salt formation (in the form of water- or oil- soluble or dispersible products) include the conventional non-toxic salts or the quaternary ammonium salts of these compounds, which are formed, e.g.; from inorganic or organic acids or bases.

In preferred embodiments, a compound of the present invention is administered in combination or alternation with AZT, D4T, FTC (2',3'-dideoxy-3'-thia-5-fluorocytidine); 3TC (Epivir, Glaxo Wellcome, Inc.), AZDU (3'-Azido-2',3'-dideoxyuridine); 141W94 (amprenavir, GlaxoWellcome, Inc.); Viramune (nevirapine), Rescriptor (delavirdine); or DMP-266 (efavirenz). Other examples of antiviral agents that can be used in combination or alternation with the compounds disclosed herein for HIV therapy include DDI, DDC, Delaviridine, β-LddA, β-L-3'-azido-d5FC, carbovir, acyclovir, interferon, stavudine, CS-92 (3'-azido-2',3'-dideoxy-5-methyl-cytidine), 3'-azido nucleosides, and β-D-dioxolane nucleosides such as β-D-dioxolanylguanine (DXG), β-D-dioxolanyl-2,6-diaminopurine (DAPD), and β-D-dioxolanyl-6-chloropurine (ACP).

Preferred protease inhibitors include indinavir ({1(1,S,2R),5(S)]-2,3,5-trideoxy-N-(2,3-dihydro-2-hydroxy-1H-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl)-D-erythro-pentoamide sulfate; Merck), nelfinavir (Agouron), ritonavir (Abbot), and saquinavir (Invirase; Roche).

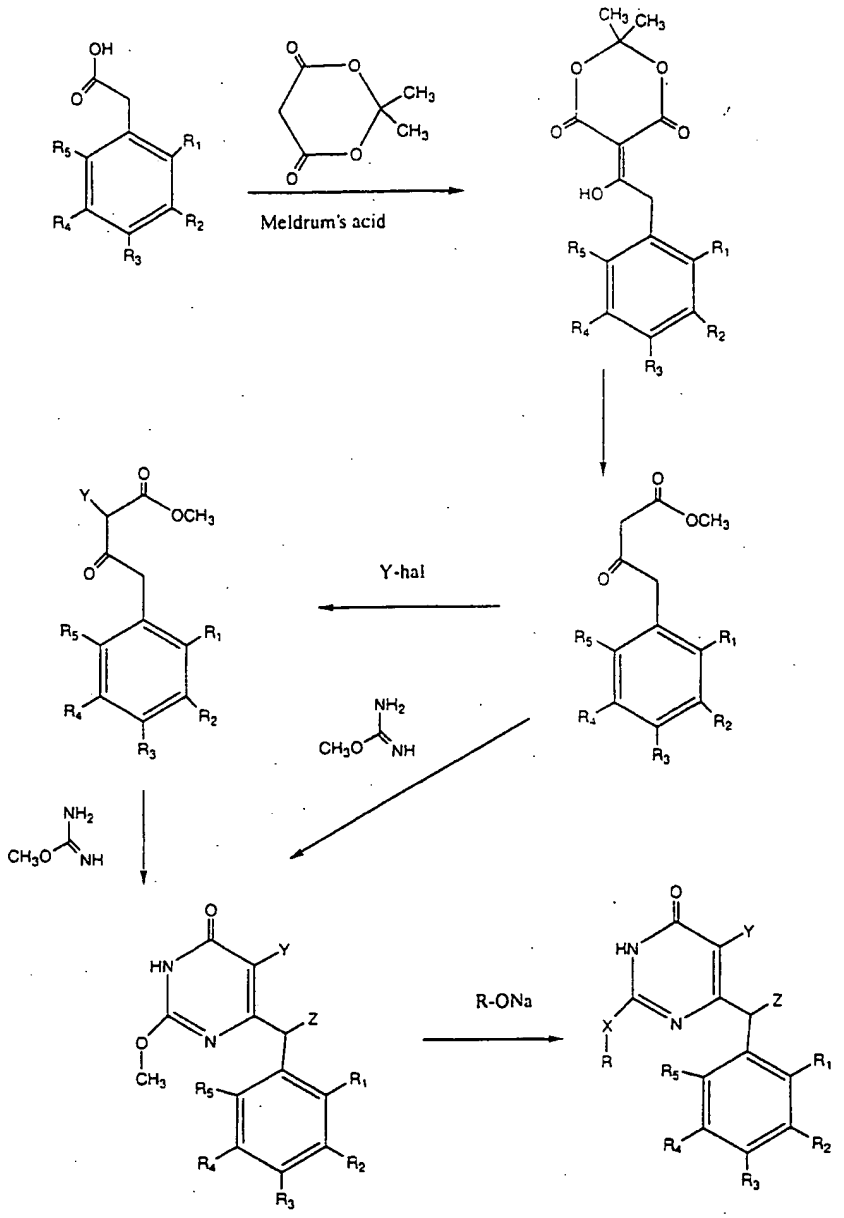
Nonlimiting examples of other compounds that can be administered in combination or alternation with the compounds of the present invention to augment the properties of the drug on administration include abacavir: (1S,4R)-4-[2-amino-6-cyclopropyl-amino)-9H-purin-9-yl]-2-cyclopentene-1-methanol succinate (1592U89, a carbovir analog; Glaxo Wellcome); zidovudine: AZT, 3'-azido-3'-deoxythymidine (Glaxo Wellcome); BILA 1906: N-{1S-[[[3-[2S-{(1,1-dimethylethyl)amino]carbonyl}-4R-]3-pyridinylmethyl)thio]-1-piperidinyl]-2R-hydroxy-1S-(phenylmethyl)propyl]amino]carbonyl]-2-methylpropyl}-2-quinolinecarboxamide (Bio Mega/Boehringer-Ingelheim); BILA 2185: N-(1,1-dimethylethyl)-1-[2S-[[2-2,6-dimethylphenoxy)-1-oxoethyl]amino]-2R-hydroxy-4-phenylbutyl]4R-pyridinylthio)-2-piperidinecarboxamide (Bio Mega/Boehringer-Ingelheim); BM+51.0836:triazoloisoindolinone derivative; BMS 186,318: aminodiol derivative HIV-1 protease inhibitor (Bristol-Myers-Squibb); d4API: 9-[2,5-dihydro-5-(phosphonomethoxy)-2-furanel]adenine (Gilead); stavudine: d4T, 2',3'-didehydro-3'-deoxythymidine (Bristol-Myers-Squibb); efavirenz: DMP-266, a 1,4-dihydro-2H-3, 1-benzoxazin-2-one; HBY097: S-4-

isopropoxycarbonyl-6-methoxy-3-(methylthio-methyl)-3,4-dihydroquinoxalin-2(1H)-thione; HEPT: 1-[(2-hydroxyethoxy)methyl]6-(phenylthio)thymine; KNI-272: (2S,3S)-3-amino-2-hydroxy-4-phenylbutyric acid-containing tripeptide; L-697,593; 5-ethyl-6-methyl-3-(2-phthalimido-ethyl)pyridin-2(1H)-one; L-735,524: hydroxy-aminopentane amide HIV-1 protease inhibitor (Merck); L-697,661: 3-{[(-4,7-dichloro-1,3-benzoxazol-2-yl)methyl]amino}-5-ethyl-6-methylpyridin-2(1H)-one; L-FDDC: (-)-β-L-5-fluoro-2',3'-dideoxycytidine; L-FDOC: (-)-β-L-5-fluoro-dioxolane cytosine; 6-benzyl-1-ethoxymethyl-5-isopropyluracil (I-EBU; Triangle/Mitsubishi); nevirapine: 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyridol[3,2-b:2',3'-e]diazepin-6-one (Boehringer-Ingelheim); PFA: phosphonoformate (foscarnet; Astra); PMEA: 9-(2-phosphonylmethoxyethyl) adenine (Gilead); PMPA: (R)-9-(2-phosphonyl-methoxypropyl)adenine (Gilead); Ro 31-8959: hydroxythethylamine derivative HIV-1 protease inhibitor (Roche); RPI-3121: peptidyl protease inhibitor, 1-[(3s)-3-(n-alpha-benzyloxycarbonyl)-1-asparginyl)-amino-2-hydroxy-4-phenylbutyryl]-n-tert-butyl-1-proline amide; 2720: 6-chloro-3,3-dimethyl-4-(isopropenyloxycarbonyl)-3,4-dihydro-quinoxalin-2(1H)thione; SC-52151: hydroxyethylurea isostere protease inhibitor (Searle); SC-55389A: hydroxyethyl-urea isostere protease inhibitor (Searle); TIBO R82150: (+)-(5S)-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]-benzodiazepin-2(1H)-thione (Janssen); TIBO 82913: (+)-(5S)-4,5,6,7,-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1jk]-[1,4]benzodiazepin-2(1H)-thione (Janssen); TSAO-m3T:[2',5'-bis-O-(tert-butyldimethylsilyl)-3'-spiro-5'-(4'-amino-1',2'-oxathiole-2',2'-dioxide)]- β-D-pentofuranosyl-N3-methylthymine; U90152: 1-[3-[(1-methylethyl)-amino]2-pyridinyl]-4-[[5-[(methylsulphonyl)-amino]-1H-indol-2yl]carbonyl]piperazine; UC: thiocarboxanilide derivatives (Uniroyal); UC-781 =N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-furancarbothioamide; UC-82 = N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2-methyl-3-thiophenecarbothioamide; VB 11,328: hydroxyethylsulphonamide protease inhibitor (Vertex); VX-478: amprenavir, 141W94, hydroxyethylsulphonamide protease inhibitor (Vertex/Glaxo Wellcome); XM 323: cyclic urea protease inhibitor (Dupont Merck), delaviridine (Pharmacia Upjohn), famciclovir, gancyclovir, and penciclovir. In another embodiment,a compound of the present invention is administered in combination with LG1350, which has the following structure.



Preparation Of Methyl Arylacetylalkylacetates

SCHEME A



Anhydrous pyridine (400 mmoles, 32.5 ml) was added with stirring under nitrogen atmosphere into an ice-cooled solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (165 mmoles, 23.75 g) in anhydrous dichloromethane (50 ml). The resulting solution was treated, over a 2 h period at 0°C under nitrogen atmosphere, with a solution of crude arylacetyl chloride in anhydrous dichloromethane (50 ml). Arylacetyl chloride was prepared before use by refluxing the proper arylacetic acid (43.2 mmoles) with thionyl chloride (21.3 ml) under nitrogen atmosphere for 2 h. Then, the mixture was stirred for 2 h at room temperature, poured into crushed ice and treated with 2N HCl (100 ml). The organic layer was separated and the aqueous solution was extracted twice with dichloromethane (25 ml). The organic phase and the extracts were combined, washed with brine, dried and evaporated. The solid residue was dissolved in anhydrous methanol (250 ml) and the solution was refluxed for 20 h. After cooling, metal sodium (0.16 g-atoms, 3.68 g) was carefully added and the mixture was stirred until dissolution was complete. Alkyl halide (160 mmoles) was dropped into the solution and the resulting mixture was heated at reflux for 4-12 h. After cooling, the solvent was removed and the residue treated with water (200 ml) and extracted with chloroform (3 x 100 ml). The organic layer was washed with brine (2 x 100 ml), dried and evaporated to give the desired compound, which was purified by passing through a silica gel column (chloroform as eluent).

In the above reaction, arylacetic acid (Scheme "A") or arylacetyl chloride can be replaced with the corresponding 1-arylacetylimidazolide (Scheme "B") or with arylacetylethoxycarbonylanhydride, whereas the Meldrum's acid can be replaced with ethyl acetylacetate, ethyl alkylmalonate or ethyl alkylmalonate potassium salt, to give the proper ethyl arylacetylalkylacetates in high yields.

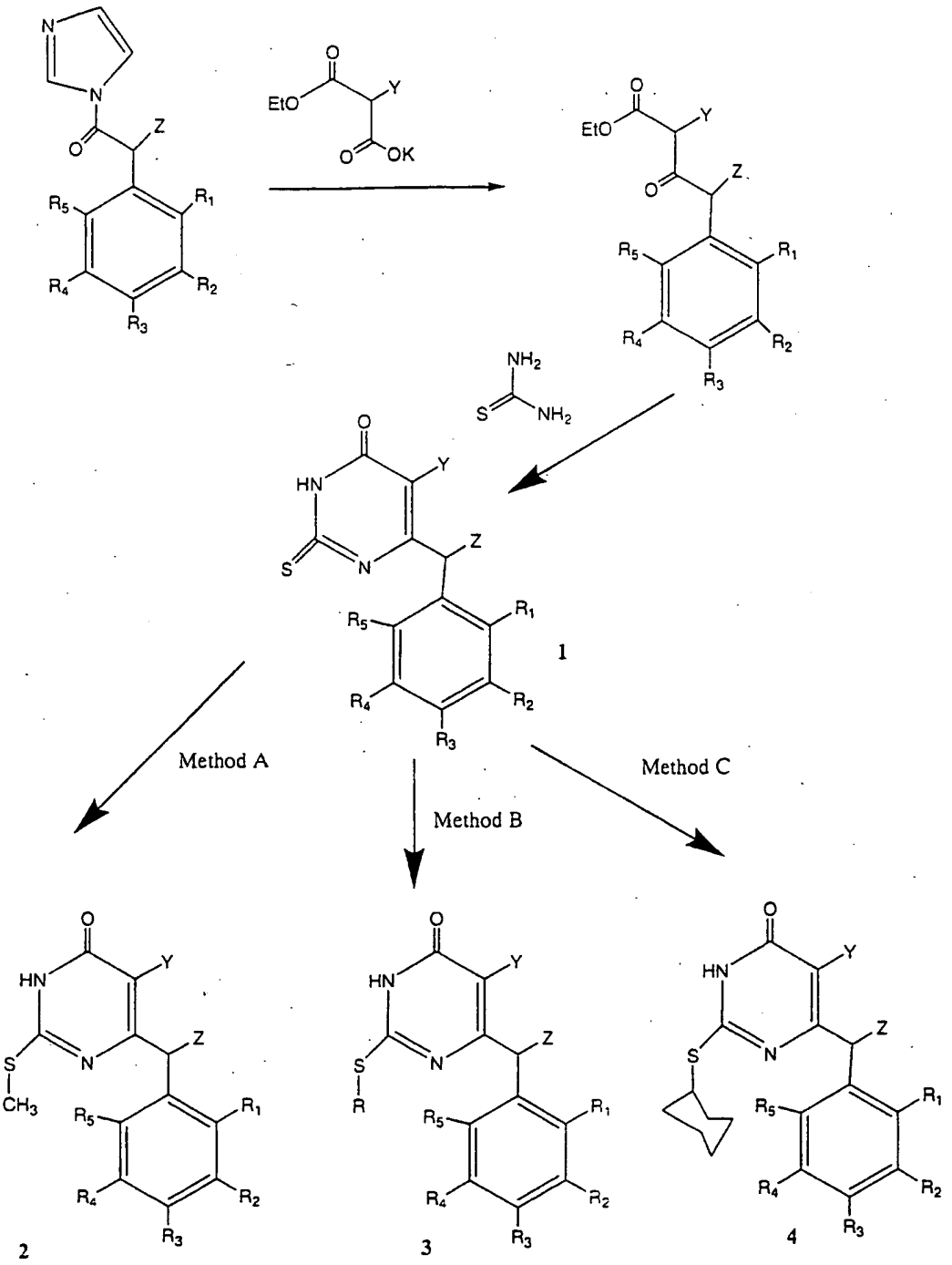
Preparation Of Compounds (I) With X = O (Scheme A).

The proper methyl arylacetylalkylacetate (10 mmoles) in methanol (50 ml) was added to a well-stirred suspension of O-methylisourea hydrogen sulphate (15 mmoles, 2.58 g) and calcium hydroxide (16 mmoles, 1.18 g) in water (50 ml). The resulting mixture was stirred at room temperature for 72 h, then concentrated, made acid (pH 5) with 0.5N acetic acid and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed with brine (100 ml), dried and evaporated to dryness. The residue was purified by crystallization

from the proper solvent yielding pure 5-alkyl-6-benzyl-3,4-dihydro-2-methoxypyrimidin-4-one. This compound was then refluxed with the proper potassium alkoxide (100 mmoles of potassium metal in 20-30 ml of alcohol freshly distilled on sodium metal) under nitrogen atmosphere until starting material disappeared at the TLC control. After cooling, the mixture was concentrated, made acid (pH 5) with 0.5N acetic acid and extracted with ethyl acetate (3 x 50 ml). The combined extracts were washed once with brine (100 ml), dried and evaporated to give the required 2-alkoxy-5-alkyl-6-benzyl-3,4-dihydropyrimidin-4-one derivative, which was recrystallized from a suitable solvent or purified by column chromatography (silica gel; ethyl acetate:chloroform 1:1). Physical and chemical data of representative compounds of the invention are reported in table 1; cytotoxicity and anti-HIV-1 activity data are reported in table 2.

Preparation Of Compounds (I) With X = S

SCHEME B



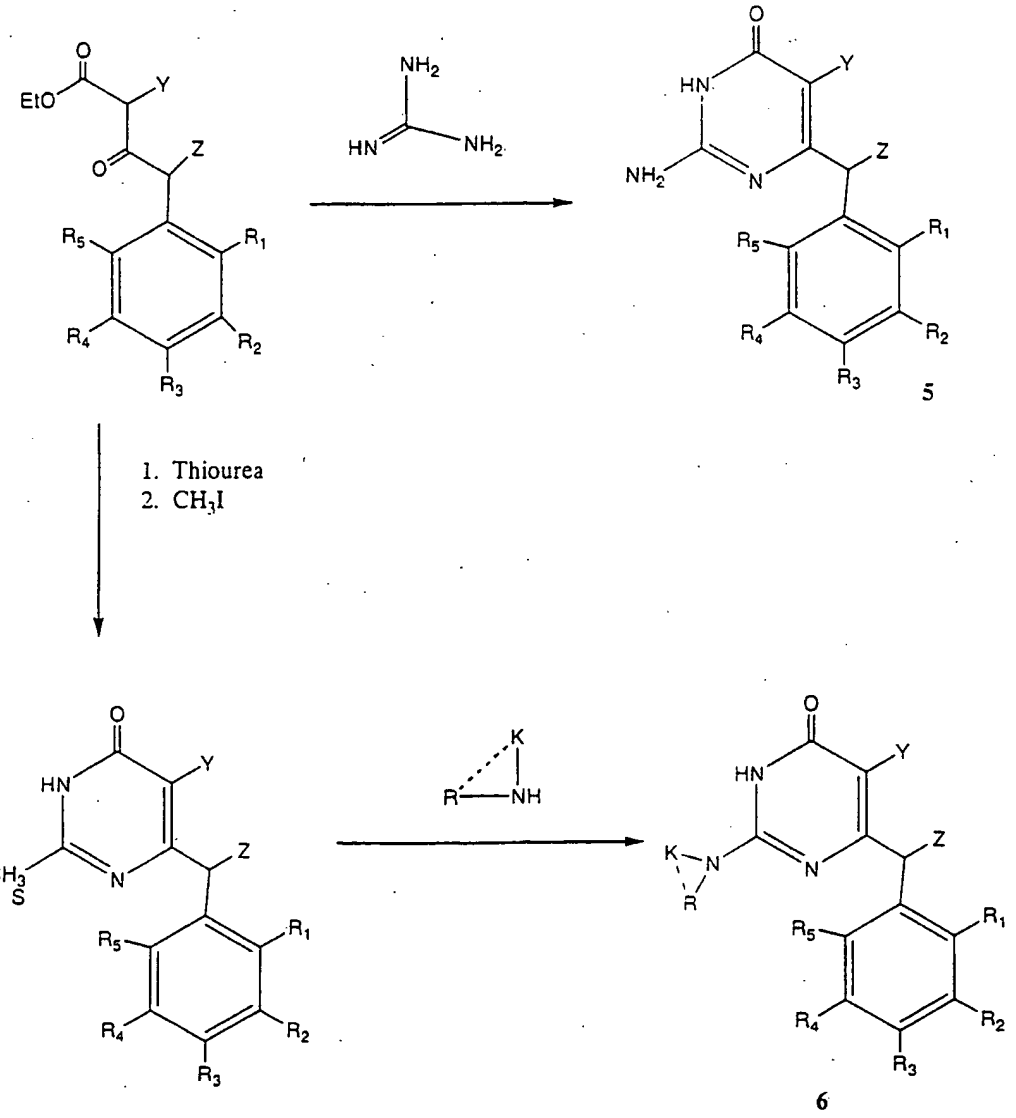
The proper ethyl arylacetylalkylacetate (31.5 mmoles) was successively added to a stirred solution of sodium metal (0.063 g-atoms) in 50 mL of absolute ethanol (50 ml) thiourea (43 mmoles). The mixture was heated while stirring at reflux for 5 h. After cooling, the solvent was distilled *in vacuo* at 40-50°C until dryness and the residue was dissolved in water (200 mL) and made acid (pH 5) with 0.5N acetic acid. The resulting precipitate (the crude 2-thiouracil derivative) was filtered under reduced pressure, washed with diethyl ether, vacuum dried at 80°C for 12 h and then crystallized from the proper solvent.

Then, according to method A, iodomethane (8 mmoles, 1.13 g) was added to a suspension containing the proper 2-thiouracil derivative (4 mmoles) in anhydrous N,N-dimethylformamide (2 ml), and the resulting mixture was stirred at room temperature until the starting material disappeared at the TLC control (silica gel; n-hexane: ethyl acetate: methanol 12:3:1). Then the reaction content was poured on cold water (100 mL) and extracted with ethyl acetate (3 x 50 ml). The organic layers were collected, washed with a sodium thiosulfate solution (100 ml), brine (3 x 50 ml), dried and evaporated to furnish the crude 5-alkyl-6-benzyl-3,4-dihydro-2-methylthiopyrimidin-4-one (2) as a solid purified by crystallization.

Alternatively, according to methods B and C, potassium carbonate (4.2 mmoles) and the proper alkyl halide (4.4 mmoles) were added to a suspension containing 2-thiouracil derivative (4 mmoles) in anhydrous N,N-dimethylformamide (2 ml). The resulting mixture was stirred at room temperature (method B) or at 80°C (method C) until starting material disappeared at the TLC control (silica gel; n-hexane:ethyl acetate:methanol 12:3:1). Then the reaction content was poured on cold water (200 mL), made acid (pH 5) with 0.5N acetic acid and extracted with ethyl acetate (3 x 50 ml). The organic layers were collected, washed with a sodium thiosulfate solution (100 ml), brine (100 ml), dried and evaporated to furnish 5-alkyl-6-benzyl-3,4-dihydro-2-methylthiopyrimidin-4-ones (3) and (4) as crude material which was then purified by column chromatography on silica gel (eluent: n-hexane:ethyl acetate:methanol 12:3:1) followed by crystallization. Physical and chemical data of representative compounds of the invention are reported in table 1. Cytotoxicity and anti-HIV-1 activity in vitro are reported in table 2.

Preparation Of Compounds (I) With X = NK

SCHEME C



Title derivatives were prepared according to the procedure described for the synthesis of compounds with X = S (I), using ethyl arylacetylalkylacetates and guanidine [2-amino-6-benzylpyrimidin-4-ones (5)] as starting materials. 2-Alkylaminoderivatives (6) were synthesized by heating the previously reported 5-alkyl-6-benzyl-3,4-dihydro-2-methylthio pyrimidin-4-ones with 20-30 ml of proper amine in a sealed tube at 170°C for 24 h. Physical and chemical data of some compounds (6) are reported in table 1. Cytotoxicity and anti-HIV-1 activity in vitro are reported in table 2. The compounds of the present invention are useful in the inhibition of HIV reverse transcriptase, the prevention or treatment of infection by the human immunodeficiency virus (HIV) and the treatment of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, organ transplant, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

The compounds of this invention are also useful in the preparation and execution of screening for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antiviral to HIV reverse transcriptase e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes. For inhibition of HIV reverse transcriptase, the prevention or treatment of infection by HIV and the treatment of AIDS or ARC, the compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of the present invention. These

pharmaceutical compositions may be in the form of orally administrable suspensions or tablets; nasal sprays; sterile injectable preparations, for example, as sterile injectable aqueous or oleagenous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweetners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these compositions may be prepared by mixing the drug with a suitable non-irritating excipient; such as cocoa buffer, synthetic glyceride, esters or polyethylene glycols, which are solid at ordinary temperatures, but liquidity and/or dissolve in the rectal cavity to release the drug.

The compounds of this invention can be administered orally to humans in a dosage range of 1 to 75 mg/kg body weight. One preferred dosage range is 1 to 50 mg/kg body weight orally. Another preferred dosage range is 5 to 75 mg/kg body weight orally. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of

excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The present invention is also directed to combinations of the HIV reverse transcriptase inhibitor compounds with one or more agents useful in the treatment of AIDS. The compounds of this invention can be administered in combination with other compounds that are HIV reverse transcriptase inhibitors, and/or with compounds that are HIV protease inhibitors. When used in a combination treatment with compounds of the instant invention, dosage levels of HIV protease inhibitors of the order of 1 to 25 or 50 grams-per-day are useful in the treatment or prevention of the above-indicated conditions, with oral doses two-to-five time higher. For example, infection by HIV is effectively treated by the administration of from 5 to 25 milligrams of the HIV protease inhibitor per kilogram of body weight from one to three times per day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy. Dosages of HIV reverse transcriptase inhibitors, when used in a combination treatment with compounds of the present invention, are comparable to those dosages specified above for the present compounds. It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals includes any combination with any pharmaceutical composition useful for the treatment of AIDS.

ANTIVIRAL ASSAY PROCEDURES

Compounds. Compounds were solubilized in DMSO at 200 mM and then diluted into culture medium.

Cells and viruses. MT-4, C8166, H9/IIIB and CEM cells were grown at 37 °C in a 5% CO_2 atmosphere in RPMI 1640 medium, supplemented with 10% fetal calf serum (FCS), 100 IU/mL penicillin and 100 µg/mL streptomycin. Cell cultures were checked periodically for the absence of mycoplasma contamination with a MycoTect Kit (Gibco). Human

immunodeficiency virus type-1 (HIV-1, III_B strain) was obtained from supernatants of persistently infected $H9/III_B$ cells. HIV-1 stock solution had a titres of $4.5x10^6$ 50% cell culture infectious dose ($CCID_{50}$)/ml.

HIV titration. Titration of HIV was performed in C8166 cells by the standard limiting dilution method (dilution 1:2, four replica wells per dilution) in 96-well plates. The infectious virus titre was determined by light microscope scoring of cytopathicity after 4 days of incubation and the virus titres were expressed as $CCID_{50}$/mL.

Anti-HIV assays. Activity of the compounds against HIV-1 and HIV-2 multiplication in acutely infected cells was based on the inhibition of virus-induced cytopathicity in MT-4 and C8166 cells, respectively. Briefly, 50 µL of culture medium containing $1x10^4$ cells were added to each well of flat-bottom microtiter trays containing 50 µl of culture medium with or without various concentrations of the test compounds. Then 20 µL of an HIV suspension containing 100 $CCID_{50}$ were added. After a 4-day incubation at 37 °C, the number of viable cells was determined by the 3-(4,5-dimethylthiazol-1-yl)-2,5-diphenyltetrazolium bromide (MTT) method. Cytotoxicity of the compounds was evaluated in parallel with their antiviral activity. It was based on the viability of mock-infected cells, as monitored by the MTT method.

RT assays. Assays were performed as follows. Briefly, purified rRT was assayed for its RNA-dependent polymerase-associated activity in a 50 µL volume containing: 50 mM TrisHCl (pH 7.8), 80 mM KCll, 6mM MgCl2, 1 mM DTT, 0.1 mg/ mL BSA, 0.3 OD_{260} unit/mL template:primer [poly(rC)-oligo(dG)12-18] and 10 µM [^{3}H]dGTP (1 Ci/mmol). After incubation for 30 min at 37 °C, the samples were spotted on glass fiber filters (Whatman GF/A), and the acid-insoluble radioactivity was determined.

EXAMPLES

2-Cyclopentylthio-6-(2,6-difluorophenylmethyl)-3,4-dihydrogyrimidin-4-(3H)-one (MC867). A mixture of 6-(2,6-difluorophenylmethyl)-1,2,3,4-tetrahydro-2-thiopyrimidin-4(3H)-one (0.16 g, 0.65 mmol; prepared as reported in scheme B), cyclopentyl bromide (0.11 g, 0.08 mL., 0.71 mmol) and potassium carbonate (0.09 g, 0.65 mmol) in 1 mL of anhydrous DMF was stirred at room temperature for 24 h. After treatment with cold water (200 mL), the solution was extracted with ethyl acetate (3 x 50 mL). The organic layers were collected, washed with brine (3 x 50 mL), dried and evaporated to furnish crude MC867, which was

purified by chromatography on silica gel column (eluent: n-hexane/ethyl acetate/methanol 12/3/1).

Yield (%): 45; mp (°C): 168-169; recrystallization solvent: cyclohexane; formula (molecula-weight): $C_{16}H_{16}F_2N_2OS$ (322.37).

2-Cyclopenylthio-6-(2,6-difluorophenylmethyl)-3,4-dihydro-5-methylpyrimidin-4-(3H)-one (MC922).

The synthesis of MC922 was accomplished according to the above reported procedure starting from 6-(2,6-difluorophenylmethyl)-5-methyl-1,2,3,4-tetrahydro-2-thiopyrimidin-4-(3H)-one (see scheme B).

Yield (%): 54; mp (°C): 192-193; recrystallization solvent: cyclohexane; formula (molecular weight): $C_{17}H_{18}F_2N_2OS$ (336.40).

2-Cyclopentylthio-6-[1-(2,6-difluorophenyl)ethyl]-3,4-dihydropyrimidin-4-(3*H*)-one (MC1008)

The synthesis of MC1008 was accomplished according to the above reported procedure starting from 6-[1-(2,6-difluorophenyl)ethyl]-1,2,3,4-tetrahydro-2-thiopyrimidin-4(3*H*)-one (see scheme B).

Yield (%): 54; mp (°C): 165.5-166.5; recrystallization solvent: cyclohexane; formula (molecular weight): $C_{17}H_{18}F_2N_2OS$ (336.40).

2-Cyclopentylthio-6-[1-(2,6-difluorophenyl)ethyl]-3,4-dihydro-5-methylpyrimidin4(3*H*)-one (MC1047)

The synthesis of MC1047 was accomplished according to the above reported procedure, starting from 6-[1-(2,6-difluorophenyl)ethyl]-5-methyl-1,2,3,4-tetrahydro-2-thiopyrimidin-4(3*H*)-one (see scheme B).

Yield (%): 60; mp (°C): 196-197; recrystallization solvent: cyclohexane; formula (molecular weight): $C_{18}H_{20}F_2N_2OS$ (350.43).

6-(2,6-Difluorophenylmethyl)-3,4-dihydro-2-(methylthiomethyl)thiopyrimidin-4-(3*H*)-one (MC1161)

The synthesis of MC1161 was accomplished according to the above reported procedures, starting from 6-(2,6-difluorophenylmethyl)-1,2,3,4-tetrahydro-2-thiopyrimidin-4(3*H*)-one (see scheme B) and chloromethyl methyl sulfide.

Yield (%): 72; mp (°C): 159-160; recrystallization solvent: benzene/cyclohexane; formula (molecular weight): $C_{13}H_{12}F_2N_2OS_2$ (314.37).

6-(2,6-Difluorophenylmethyl)-3,4-dihydro-5-methyl-2-(methylthiomethyl)thiopyrimidin-4(3H)-one (MC1162).

The synthesis of MC1162 was accomplished according to the above reported procedure, starting from 6-(2,6-difluorophenylmethyl)-5-methyl-1,2,3,4-tetrahydro-2-thiopyrimidin 4(3*H*)-one (see scheme B) and chloromethyl methyl sulfide.

Yield (%): 70; mp (°C): 183-184; recrystallization solvent: benzene/cyclohexane; formula (molecular weight): $C_{14}H_{14}F_2N_2OS_2$ (328.39).

6-(2,6-Difluorophenylmethyl)-3,4-dihydro-5-(1-methylethyl)-2-(methylthiomethyl) thiopyrimidin-4-(3*H*)-one MC1145).

The synthesis of MC1145 was accomplished according to the above reported procedure, starting from 6-(2,6-difluorophenylmethyl)-5-(1-methylethyl)-1,2,3,4-tetrahydro-2-thiopyrimidin-4(3*H*)-one (see scheme B) and chloromethyl methyl sulfide.

Yield (%): 62; mp (°C): 158.5-160; recrystallization solvent: cyclohexane; formula (molecular weight): $C_{16}H_{18}F_2N_2OS_2$ (356.45).

2-Cyclopenltylamino-6-(2,6-difluorophenylmethyl)-3,4-dihydropyrimidin-4-(3H)-one (MC1022).

Cyclopentylamine (10 mL) was heated while stirring with 6-(2,6-difluorophenylmethyl)-3,4-dihydro-2-methylthiopyrimidin-4-(3*H*)-one (0.30 g, 1.12 mmol; prepared as reported in scheme B or C) in a sealed tube at 160°C for 10 h. After cooling, the mixture was diluted with water (200 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layers were collected, washed with brine (3 x 50 mL), dried and evaporated to furnish crude MC1022,

which was purified by chromatography on silica get column (eluent: ethyl acetate/chloroform 1/1).

Yield (%): 74; mp (°C): - (oil); formula (molecular weight): $C_{16}H_{17}F_2N_3O$ (305.33).

2-Cyclopentylamino-6-(2,6-difluorophenylmethyl)-3,4-dihydro-5-methylpyrimidin-4-(3*H*)-one (MC1050).

The synthesis of MC1050 was accomplished according to the above reported procedure, starting from 6-(2,6-difluorophenylmethyl)-3,4-dihydro-5-methyl-2-methylthiopyrimidirin-4(3*H*)-one (see scheme B or C).

Yield (%): 60; mp (°C): 115-117; recrystallization solvent: n-hexane/cyclohexane; formula (molecular weight): $C_{17}H_{19}F_2N_3O$ (319.35).

2-Cyclopentylamino-6-[1-(2,6-difluorophenyl)ethyl]-3,4-dihydropyrimidin-4-(3*H*)-one (MC1048).

The synthesis of MC1048 was accomplished according to the above reported procedure, starting from 6-[1-(2,6-difluorophenyl)ethyl]-3,4-dihydro-2-methylthiopyrimidin-4(3*H*)-one (see scheme B or C).

Yield (%): 48; mp (°C): - (oil); formula (molecular weight) $C_{17}H_{19}F_2N_3O$ (319.35).

2-Cyclopentylamino-6-[1-(2,6-difluorophenyl)ethyl]-3,4-dihydro-5-methylpyrimidin-4-(3*H*)-one (MC1129)

The synthesis of MC1129 was accomplished according to the above reported procedure, starting from 6-[1-(2,6-difluorophenyl)ethyl]-3,4-dihydro-5-methyl-2-methylthiopyrimidin-4(3*H*)-one (see scheme B or C).

Yield (%): 38; mp (°C): - (oil); formula (molecular weight): $C_{18}H_{21}F_2N_3O$ (333.38).

6-(2,6-Difluorophenylmethyl)-3,4-dihydro-2-(4-thiomorpholin-1-yl)pyrimidin-4-(3*H*)-one (MC1193).

The synthesis of MC1193 was accomplished according to the above reported procedure, starting from thiomorpholine and 6-(2,6-difluorophenylmethyl)-3,4-dihydro-2-methylthiopyrimidin-4(3*H*)-one (see scheme B or C).

Yield (%): 78; mp (°C): 233-234; recrystallization solvent: acetonitrile; formula (molecular weight): $C_{15}H_{15}F_2N_3OS$ (323.36).

6-(2,6-Difluorophenylmethyl)-3,4-dihydro-2-*N*,*N*-dimethylaminopyrimidin-4-(3*H*)-one (MC1182).

To a stirred solution of sodium metal (0.14 g, 6.3 mg-atoms) in absolute ethanol (50 mL) 1,1-dimethylguanidine sulfate (1.17 g, 4.3 mmol) and ethyl 4-(2,6-difluorophenyl)acetylacetate (0.76 g, 3.15 mmol) were successively added. The mixture was heated while stirring at reflux for 8 h. After cooling, the solvent was distilled *in vacuo* at 40-50°C until dryness and the residue was dissolved in water (200 mL) and made acid (pH 5) with 0.5N acetic acid. The resulting precipitate (the crude isocytosine derivative) was filtered under reduced pressure, washed with diethyl ether, vacuum dried at 80°C for 12 h and then crystallized from benzene/cyclohexane (see scheme C starting from ethyl 4-(2,6-difluorophenyl)acetylacetate and replacing guanidine hydrochloride with 1,1-dimethylguanidine sulfate).

Yield (%): 88; mp (°C): 210-211; recrystallization solvent: benzene/cyclohexane; formula (molecular weight): $C_{13}H_{13}F_2N_3O$ (265.26).

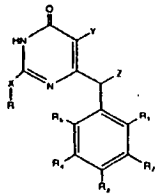


Table 1. Physical and Chemical Data of MC Compounds

Compd.	X	Y	Z	R	R^1	R^2	R^3	R^4	R^5	m.p., ° C	Recryst. Solvent	% yield	Formula [a]
MC 507	O	H	H	2,5-Me_2-c-hex	H	H	H	H	H	130-132	Petrol. Ether/diethyl ether	22	$C_{19}H_{24}N_2O_2$
MC 508	O	H	H	4,5-Me_2-c-hex	H	H	H	H	H	132-134	Petrol. Ether/diethyl ether	28	$C_{19}H_{24}N_2O_2$
MC 512	O	H	H	3,5-Me_2-c-hex	H	H	H	H	H	178-181	Petrol. Ether/diethyl ether	12	$C_{19}H_{24}N_2O_2$
MC 531	O	Me	H	2,5-Me_2-c-hex	H	H	H	H	H	196-198	Petrol. Ether/diethyl ether	18	$C_{20}H_{26}N_2O_2$
MC 1114	O	H	H	Sec-but	F	H	H	H	F	87-88	Petrol. Ether/diethyl ether	28	$C_{15}H_{16}F_2N_2O_2$
MC 1103	O	H	H	c-pent	F	H	H	H	F	183.5-184.5	Benzene	52	$C_{16}H_{16}F_2N_2O_2$
MC 843	S	H	H	benzyloxymeth	H	H	H	H	H	181-183	Cyclohexane/benzene	38	$C_{19}H_{18}N_2O_2S$
MC 796	S	H	Ph	Sec-but	H	H	H	H	H	157-158	n-hexane/cyclohexane	78	$C_{21}H_{22}N_2OS$
MC 890	S	H	Me	Iso-prop	H	H	H	H	H	118-119	n-hexane	88	$C_{15}H_{18}N_2OS$
MC 892	S	H	Me	c-pent	H	H	H	H	H	95-96	n-hexane	65	$C_{17}H_{20}N_2OS$
MC 898	S	H	Me	c-hex	H	H	H	H	H	142-143	n-hexane	59	$C_{18}H_{22}N_2OS$
MC 899	S	H	Et	Iso-prop	H	H	H	H	H	144-145	Cyclohexane	85	$C_{16}H_{20}N_2OS$
MC 900	S	H	Et	c-pent	H	H	H	H	H	168-169	Cyclohexane	69	$C_{18}H_{22}N_2OS$
MC 903	S	H	Et	c-hex	H	H	H	H	H	175.5-176.5	Cyclohexane	60	$C_{19}H_{24}N_2OS$
MC 806	S	H	H	Sec-but	Me	H	H	H	H	118-119	n-hexane/cyclohexane	67	$C_{16}H_{20}N_2OS$
MC 842	S	H	H	c-pent	Me	H	H	H	H	142-144	Cyclohexane	61	$C_{17}H_{20}N_2OS$
MC 809	S	H	H	Sec-but	H	H	Me	H	H	107.5-108.5	n-hexane	56	$C_{16}H_{20}N_2OS$
MC 817	S	H	H	Sec-but	NO_2	H	H	H	H	148.0-148.5	Cyclohexane/benzene	68	$C_{15}H_{17}N_3O_3S$
MC 897	S	H	H	Sec-but	H	NO_2	H	H	H	127-128	Cyclohexane/benzene	54	$C_{15}H_{17}N_3O_3S$
MC 863	S	H	H	Sec-but	H	H	NO_2	H	H	128-130	Petrol. Ether/diethyl ether	100	$C_{15}H_{17}N_3O_3S$
MC 854	S	H	H	Sec-but	Cl	H	H	H	H	120-121	n-hexane/cyclohexane	58	$C_{15}H_{17}N_3O_3S$
MC 857	S	H	H	Sec-but	H	Cl	H	H	H	98-99	Cyclohexane	92	$C_{15}H_{17}N_3O_3S$
MC 859	S	H	H	Sec-but	H	H	Cl	H	H	125-126	Cyclohexane	74	$C_{15}H_{17}ClN_2OS$
MC 880	S	H	H	Sec-but	F	H	H	H	H	106-107	n-hexane/cyclohexane	68	$C_{15}H_{17}ClN_2OS$
MC 884	S	H	H	Sec-but	H	F	H	H	H	96-97	Cyclohexane	67	$C_{15}H_{17}FN_2OS$
MC 889	S	H	H	Sec-but	H	H	F	H	H	98-99	n-hexane	94	$C_{15}H_{17}FN_2OS$
MC 825	S	H	H	Sec-but	NH_2	H	H	H	H	143-144	Cyclohexane/benzene	74	$C_{15}H_{19}N_3OS$
MC 960	S	H	H	Sec-but	H	H	NH_2	H	H	128-130	Cyclohexane	77	$C_{15}H_{19}N_3OS$
MC 868	S	H	H	Sec-but	CF_3	H	H	H	H	125-126	Cyclohexane	89	$C_{16}H_{17}F_3N_2OS$
MC 959	S	H	H	Sec-but	H	H	CF_3	H	H	144-145	Cyclohexane	75	$C_{16}H_{17}F_3N_2OS$
MC 952	S	H	H	Sec-but	OMe	H	H	H	H	123-124	Cyclohexane	69	$C_{16}H_{20}N_2O_2S$

Table 1. Physical and Chemical Data of MC Compounds (continued)

Compd.	X	Y	Z	R	R^1	R^2	R^3	R^4	R^5	m.p., ° C	Recryst. Solvent	% yield	Formula [a]
MC957	S	H	H	Sec-but	H	OMe	H	H	H	78-80	n-hexane/ Cyclohexane	71	$C_{16}H_{20}N_2O_2S$
MC964	S	H	H	Sec-but	H	H	OMe	H	H	112-113	Cyclohexane	63	$C_{16}H_{20}N_2O_2S$
MC1041	S	H	H	Sec-but	H	F	H	H	H	122-123	Cyclohexane	68	$C_{15}H_{16}F_2N_2OS$
MC1042	S	H	H	Sec-but	H	Me	H	H	H	119-120	n-hexane	72	$C_{17}H_{22}N_2OS$
MC877	S	H	H	Me	Cl	H	H	H	Cl	237-238	benzene	98	$C_{12}H_{10}Cl_2N_2OS$
MC878	S	H	H	iso-prop	Cl	H	H	H	Cl	230-231	benzene	81	$C_{14}H_{14}Cl_2N_2OS$
MC886	S	H	H	n-but	Cl	H	H	H	Cl	153-154	cyclohexane	62	$C_{15}H_{16}Cl_2N_2OS$
MC885	S	H	H	iso-but	Cl	H	H	H	Cl	143.5-144.5	cyclohexane	56	$C_{15}H_{16}Cl_2N_2OS$
MC815	S	H	H	sec-but	Cl	H	H	H	Cl	183-184	cyclohexane/benzene	55	$C_{15}H_{16}Cl_2N_2OS$
MC888	S	H	H	c-pent	Cl	H	H	H	Cl	185-186	cyclohexane	54	$C_{16}H_{16}Cl_2N_2OS$
MC891	S	H	H	c-hex	Cl	H	H	H	Cl	200-201	cyclohexane/benzene	49	$C_{17}H_{18}Cl_2N_2OS$
MC871	S	H	H	Me	F	H	H	H	F	197-198	benzene	95	$C_{12}H_{10}F_2N_2OS$
MC860	S	H	H	iso-prop	F	H	H	H	F	174-175	cyclohexane	74	$C_{14}H_{14}F_2N_2OS$
MC872	S	H	H	n-but	F	H	H	H	F	126-127	cyclohexane	46	$C_{15}H_{16}F_2N_2OS$
MC866	S	H	H	iso-but	F	H	H	H	F	136-137	cyclohexane	49	$C_{15}H_{16}F_2N_2OS$
MC848	S	H	H	sec-but	F	H	H	H	F	149-150	n-hexane/cyclohexane	48	$C_{15}H_{16}F_2N_2OS$
MC867	S	H	H	c-pent	F	H	H	H	F	168-169	cyclohexane	45	$C_{16}H_{16}FN_2OS$
MC870	S	H	H	c-hex	F	H	H	H	F	164-165	cyclohexane	40	$C_{17}H_{18}F_2N_2OS$
MC1001	S	H	Me	iso-prop	Cl	H	H	H	Cl	196-196.5	cyclohexane/benzene	52	$C_{15}H_{16}Cl_2N_2OS$
MC996	S	H	Me	c-pent	Cl	H	H	H	Cl	181-182	cyclohexane	45	$C_{17}H_{18}Cl_2N_2OS$
MC1016	S	H	Me	c-hex	Cl	H	H	H	Cl	211-212	cyclohexane/benzene	42	$C_{18}H20Cl_2N_2OS$
MC1000	S	H	Et	iso-prop	Cl	H	H	H	Cl	166-168	diethyl ether	54	$C16H_{18}Cl_2N_2OS$
MC1002	S	H	Et	c-pent	Cl	H	H	H	Cl	168-169	diethyl ether	40	$C_{18}H_{20}Cl_2N_2OS$
MC1003	S	H	Et	c-hex	Cl	H	H	H	Cl	198-199	cyclohexane	41	$C_{19}H_{22}Cl_2N_2OS$
MC1007	S	H	Me	iso-prop	F	H	H	H	F	155-156	cyclohexane	53	$C_{15}H_{16}F_2N_2OS$
MC1044	S	H	Me	iso-but	F	H	H	H	F	159-160	cyclohexane	49	$C_{16}H_{18}F_2N_2OS$
MC1045	S	H	Me	n-but	F	H	H	H	F	149-150	cyclohexane	58	$C_{16}H_{18}F_2N_2OS$
MC1110	S	H	Me	sec-but	F	H	H	H	F	133-134	n-hexane	75	$C_{16}H_{18}F_2N_2OS$
MC1008	S	H	Me	c-pent	F	H	H	H	F	165.5-166.5	cyclohexane	60	$C_{17}H_{18}F_2N_2OS$
MC1013	S	H	Me	c-hex	F	H	H	H	F	206-207	benzene	44	$C_{18}H_{20}F_2N_2OS$
MC1005	S	H	Et	iso-prop	F	H	H	H	F	149-150	cyclohexane	40	$C_{16}H_{18}F_2N_2OS$
MC1006	S	H	Et	c-pent	F	H	H	H	F	141-143	cyclohexane	45	$C_{18}H_{20}F_2N_2OS$
MC1014	S	H	Et	c-hex	F	H	H	H	F	154-155	cyclohexane	51	$C_{19}H_{22}F_2N_2OS$
MC971	S	H	Me	iso-prop	CH=CH-CH=CH		H	H	H	161-162	n-hexane/cyclohexane	58	$C_{19}H_{20}N_2OS$
MC972	S	H	Me	c-pent	CH=CH-CH=CH		H	H	H	140-141	n-hexane/cyclohexane	49	$C_{21}H_{22}N_2OS$
MC974	S	H	Me	c-hex	CH=CH-CH=CH		H	H	H	177-178	n-hexane	45	$C_{22}H_{24}N_2OS$
MC969	S	H	Et	iso-prop	CH=CH-CH=CH		H	H	H	163-164	cyclohexane	54	$C_{20}H_{22}N_2OS$
MC973	S	H	Et	c-pent	CH=CH-CH=CH		H	H	H	oil	--	48	$C_{22}H_{24}N_2OS$
MC975	S	H	Et	c-hex	CH=CH-CH=CH		H	H	H	126-127	n-hexane	41	$C_{23}H_{26}N_2OS$
MC844	S	Me	H	sec-but	Me	H	H	H	H	177-178	cyclohexane	55	$C_{17}H_{22}N_2OS$
MC845	S	Me	H	sec-but	H	H	Me	H	H	127-128	n-hexane	61	$C_{17}H_{22}N_2OS$
MC925	S	Me	H	sec-but	H	NO_2	H	H	H	163-164	cyclohexane/benzene	88	$C_{16}H_{19}N_3O_3S$
MC924	S	Me	H	sec-but	H	H	NO_2	H	H	178-180	cyclohexane/benzene	100	$C_{16}H_{19}N_3O_3S$
MC909	S	Me	H	sec-but	Cl	H	H	H	H	170-171	cyclohexane	68	$C_{16}H_{19}ClN_2OS$

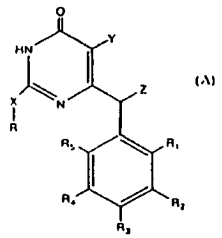
Table 1. Physical and Chemical Data of MC Compounds (continued)

Compd.	X	Y	Z	R	R^1	R^2	R^3	R^4	R^5	m.p., ° C	Recryst. Solvent	% yield	Formula [a]
MC910	S	Me	H	sec-but	H	Cl	H	H	H	145-146	cyclohexane	75	$C_{16}H_{19}ClN_2OS$
MC911	S	Me	H	sec-but	H	H	Cl	H	H	163-165	cyclohexane	79	$C_{16}H_{19}ClN_2OS$
MC913	S	Me	H	sec-but	F	H	H	H	H	120.5-121.5	cyclohexane	65	$C_{16}H_{19}FN_2OS$
MC918	S	Me	H	sec-but	H	F	F	H	H	146-147	cyclohexane	72	$C_{16}H_{18}FN_2OS$
MC919	S	Me	H	sec-but	H	H	H	H	H	154-155	cyclohexane	69	$C_{16}H_{19}FN_2OS$
MC912	S	Me	H	Me	Cl	H	H	H	Cl	206-261	benzene	93	$C_{13}H_{12}Cl_2N_2OS$
MC914	S	Me	H	iso-prop	Cl	H	H	H	Cl	241-242	cyclohexane/benzene	78	$C_{15}H_{16}Cl_2N_2OS$
MC920	S	Me	H	n-but	Cl	H	H	H	Cl	179-180	cyclohexane	52	$C_{16}H_{18}Cl_2N_2OS$
MC916	S	Me	H	iso-but	Cl	H	H	H	Cl	208-209	cyclohexane	63	$C_{16}H_{18}Cl_2N_2OS$
MC850	S	Me	H	sec-but	Cl	H	H	H	Cl	204-205	cyclohexane	53	$C_{16}H_{18}Cl_2N_2OS$
MC915	S	Me	H	c-pent	Cl	H	H	H	Cl	252-253	cyclohexane/benzene	49	$C_{17}H_{18}Cl_2N_2OS$
MC917	S	Me	H	c-hex	Cl	H	H	H	Cl	237-238	cyclohexane	48	$C_{18}H_{20}Cl_2N_2OS$
MC869	S	Me	H	Me	F	H	H	H	F	218.5-219.5	benzene	92	$C_{13}H_{12}F_2N_2OS$
MC881	S	Me	H	iso-prop	F	H	H	H	F	164-165	cyclohexane	76	$C_{15}H_{16}F_2N_2OS$
MC905	S	Me	H	n-but	F	H	H	H	F	178-179	cyclohexane	65	$C_{16}H_{18}F_2N_2OS$
MC921	S	Me	H	iso-but	F	H	H	H	F	161-162	cyclohexane	59	$C_{16}H_{18}F_2N_2OS$
MC849	S	Me	H	sec-but	F	H	H	H	F	128-129	n-hexane	49	$C_{16}H_{18}F_2N_2OS$
MC922	S	Me	H	c-pent	F	H	H	H	F	192-193	cyclohexane	54	$C_{17}H_{18}F_2N_2OS$
MC923	S	Me	H	c-hex	F	H	H	H	F	191-192	cyclohexane	49	$C_{18}H_{20}F_2N_2OS$
MC1060	S	Me	Me	Me	F	H	H	H	F	202-203	cyclohexane/benzene	49	$C_{14}H_{14}F_2N_2OS$
MC1109	S	Me	Me	sec-but	F	H	H	H	F	135-136	cyclohexane	55	$C_{17}H_{20}F_2N_2OS$
MC1047	S	Me	Me	c-pent	F	H	H	H	F	196-197	cyclohexane	60	$C_{18}H_{20}F_2N_2OS$
MC798	S	Et	H	sec-but	H	H	H	H	H	140-141	n-hexane	47	$C_{17}H_{22}N_2OS$
MC1037	S	Et	H	iso-prop	F	H	H	H	F	174-175	benzene	78	$C_{16}H_{18}F_2N_2OS$
MC1038	S	Et	H	sec-but	F	H	H	H	F	150-151	n-hexane/cyclohexane	62	$C_{17}H_{20}F_2N_2OS$
MC804	S	Et	H	sec-but	CH=CH-CH=CH		H	H	H	198.5-199.5	cyclohexane	42	$C_{21}H_{24}N_2OS$
MC1039	S	i-pro	H	iso-prop	F	H	H	H	F	167-168	n-hexane	76	$C_{17}H_{20}F_2N_2OS$
MC852	S	allyl	H	sec-but	H	H	H	H	H	127.5-128.5	cyclohexane	68	$C_{18}H_{22}N_2OS$
MC856	S	n-pro	H	sec-but	H	H	H	H	H	108-109	n-hexane	42	$C_{18}H_{24}N_2OS$
MC834	S	n-but	H	sec-but	H	H	H	H	H	oil	--	32	$C_{19}H_{26}N_2OS$
MC1119	NH	H	H	ethyl	F	H	H	H	F	138-140	n-hexane/cyclohexane	50	$C_{13}H_{13}F_2N_3O$
MC1078	NH	H	H	n-prop	F	H	H	H	F	136-137	cyclohexane	49	$C_{14}H_{15}F_2N_3O$
MC979	NH	H	H	iso-prop	F	H	H	H	F	150-151	diethyl ether	58	$C_{14}H_{15}F_2N_3O$
MC980	NH	H	H	c-prop	F	H	H	H	F	183-184	cyclohexane/benzene	68	$C_{14}H_{13}F_2N_3O$
MC1077	NH	H	H	n-but	F	H	H	H	F	130-131	n-hexane	60	$C_{15}H_{17}F_2N_3O$
MC945	NH	H	H	sec-but	F	H	H	H	F	140-141	diethyl ether	80	$C_{15}H_{17}F_2N_3O$
MC1043	NH	H	H	MeOethyl	F	H	H	H	F	120-121	acetonitrile	78	$C_{14}H_{15}F_2N_3O_2$
MC1022	NH	H	H	c-pent	F	H	H	H	F	oil	--	74	$C_{16}H_{17}F_2N_3O$
MC1049	NH	H	H	c-hex	F	H	H	H	F	143-144	diethyl ether	45	$C_{17}H_{19}F_2N_3O$
MC1048	NH	H	Me	c-pent	F	H	H	H	F	oil	--	48	$C_{17}H_{19}F2N_3O$
MC1118	NH	Me	H	iso-prop	F	H	H	H	F	165-166	n-hexane	53	$C_{15}H_{17}F_2N_3O$
MC1130	NH	Me	H	sec-but	F	H	H	H	F	oil	--	56	$C_{16}H_{19}F_2N_3O$
MC1050	NH	Me	H	c-pent	F	H	H	H	F	115-117	n-hexane/cyclohexane	60	$C_{17}H_{19}F_2N_3O$
MC1105	NH	Me	H	benzyl	F	H	H	H	F	182-183	cyclohexane/benzene	82	$C_{19}H_{17}F_2N_3O$

Table 1. Physical and Chemical Data of MC Compounds (continued)

Compd.	X	Y	Z	R	R^1	R^2	R^3	R^4	R^5	m.p., ° C	Recryst. Solvent	% yield	Formula [a]
MC1129	NH	Me	Me	c-pent	F	H	H	H	F	oil	--	38	$C_{16}H_{21}F_2N_3O$
MC1167	NH	H	H	Me	F	H	H	H	F	202-203	acetonitrile	39	$C_{12}H_{11}F_2N_3O$
MC1168	NH	Me	H	Me	F	H	H	H	F	210-211	acetonitrile	48	$C_{13}H_{13}F_2N_3O$
MC1186	NH	Me	H	n-prop	F	H	H	H	F	156-157	acetonitrile	62	$C_{15}H_{17}F_2N_3O$
MC1185	NH	Me	H	n-but	F	H	H	H	F	192-193	acetonitrile	68	$C_{16}H_{19}F_2N_3O$
MC1178	NH	H	Me	Me	F	H	H	H	F	145-146	acetonitrile	34	$C_{13}H_{13}F_2N_3O$
MC1190	NH	H	Me	n-prop	F	H	H	H	F	oil	---	45	$C_{15}H_{17}F_2N_3O$
MC1191	NH	H	Me	iso-prop	F	H	H	H	F	oil	---	54	$C_{15}H_{17}F_2N_3O$
MC1189	NH	H	Me	n-but	F	H	H	H	F	oil	---	55	$C_{16}H_{19}F_2N_3O$
MC1192	NH	H	Me	sec-but	F	H	H	H	F	oil	---	59	$C_{16}H_{19}F_2N_3O$
MC1180	NH	H	Me	c-hex	F	H	H	H	F	oil	---	62	$C_{18}H_{21}F_2N_3O$
MC1170	NH	Me	Me	Me	F	H	H	H	F	193-194	cyclohexane/benzene	34	$C_{14}H_{15}F_2N_3O$
MC1187	NH	Me	Me	n-but	F	H	H	H	F	oil	---	49	$C_{17}H_{21}F_2N_3O$
MC1181	NH	Me	Me	c-hex	F	H	H	H	F	oil	---	54	$C_{19}H_{23}F_2N_3O$
MC1182	N	H	H	Me_2	F	H	H	H	F	210-211	cyclohexane/benzene	88	$C_{13}H_{13}F_2N_3O$
MC1183	N	H	H	Me-piperaz	F	H	H	H	F	195-196	acetonitrile	84	$C_{18}H_{18}F_2N_4O$
MC1188	N	H	H	morph	F	H	H	H	F	215-216	acetonitrile	75	$C_{15}H_{15}F_2N_3O_2$
MC1193	N	H	H	thiomorph	F	H	H	H	F	233-234	acetonitrile	78	$C_{15}H_{15}F_2N_3OS$
MC1194	N	H	H	piperid	F	H	H	H	F	209-210	acetonitrile	68	$C_{16}H_{17}F_2N_3O$
MC1196	N	H	H	pyrrolid	F	H	H	H	F	233-234	acetonitrile	52	$C_{15}H_{15}F_2N_3O$
MC1202	N	H	H	Et_2	F	H	H	H	F	159-160	acetonitrile	43	$C_{15}H17F_2N_3O$
MC1204	N	H	H	$(n\text{-prop})_2$	F	H	H	H	F	111-112	n-hexane	32	$C_{17}H_{21}F_2N_3O$
MC1195	N	Me	H	Me_2	F	H	H	H	F	237-238	acetonitrile	80	$C_{14}H_{15}F_2N_3O$
MC1203	N	Me	H	Me-piperaz	F	H	H	H	F	235-236	acetonitrile	62	$C_{17}H_{20}F_2N_4O$
MC1205	N	Me	H	morph	F	H	H	H	F	244-245	acetonitrile	65	$C_{16}H_{17}F_2N_3O_2$
MC1206	N	Me	H	thiomorph	F	H	H	H	F	255-256	acetonitrile	54	$C_{16}H_{17}F_2N_3OS$
MC1137	S	Me	Me	iso-prop	F	H	H	H	F	177-178	n-hexane/cyclohexane	45	$C_{16}H_{18}F_2N_2OS$
MC1175	S	Me	Me	n-but	F	H	H	H	F	122-123	n-hexane	51	$C_{17}H_{20}F_2N_2OS$
MC1153	S	Me	Me	iso-but	F	H	H	H	F	152-153	cyclohexane	58	$C_{17}H_{20}F_2N_2OS$
MC1174	S	Me	Me	c-hex	F	H	H	H	F	208-209	n-hexane/cyclohexane	48	$C_{19}H_{22}F_2N_2OS$
MC1161	S	H	H	MeSMe	F	H	H	H	F	159-160	cyclohexane/benzene	72	$C_{13}H_{12}F_2N_2OS_2$
MC1162	S	Me	H	MeSMe	F	H	H	H	F	183-184	cyclohexane/benzene	70	$C_{14}H_{14}F_2N_2OS_2$
MC1157	S	Et	H	MeSMe	F	H	H	H	F	153-154	cyclohexane	69	$C_{15}H_{16}F_2N_2OS_2$
MC1145	S	i-pro	H	MeSMe	F	H	H	H	F	158.5-160	cyclohexane	62	$C_{16}H_{18}F_2N_2OS_2$
MC1140	S	H	H	MeSMe	H	H	H	H	H	117.5-118	n-hexane	64	$C_{13}H_{14}N_2OS_2$

[a] All compounds were analyzed for C, H, N, S, and, when required, Cl and F; analytical results were within ±0.4% of theroretical values.



(A)

Table 2. Cytotoxicity and anti-HIV-1 Activity of MC Compounds.

Compd.	X	Y	Z	R	R^1	R^2	R^3	R^4	R^5	[μM] CC_{50} [b]	[μM] EC_{50} [c]	SI [d]
MC 507	O	H	H	2,5-Me_2-c-hex	H	H	H	H	H	143	3.5	40
MC 508	O	H	H	4,5-Me_2-c-hex	H	H	H	H	H	58	6.4	9
MC 512	O	H	H	3,5-Me_2-c-hex	H	H	H	H	H	>200	30	>6.7
MC 531	O	Me	H	2,5-Me_2-c-hex	H	H	H	H	H	138	3.5	39
MC 1114	O	H	H	sec-but	F	H	H	H	F	130	25	52
MC 1103	O	H	H	c-pent	F	H	H	H	F	>200	20	>10
MC 843	S	H	H	benzoyloxymethyl	H	H	H	H	H	>200	45	>4
MC 796	S	H	Ph	sec-but	H	H	H	H	H	61	>61	-
MC 890	S	H	Me	iso-prop	H	H	H	H	H	>200	.9	>222
MC 892	S	H	Me	c-pent	H	H	H	H	H	159	.6	333
MC 898	S	H	Me	c-hex	H	H	H	H	H	149	.6	248
MC 899	S	H	Et	iso-prop	H	H	H	H	H	200	.8	250
MC 900	S	H	Et	c-pent	H	H	H	H	H	>200	1.0	>200
MC 903	S	H	Et	c-hex	H	H	H	H	H	>200	1.3	>154
MC 806	S	H	H	sec-but	Me	H	H	H	H	>200	1.8	>111
MC 842	S	H	H	c-pent	Me	H	H	H	H	>200	3.4	>59
MC 809	S	H	H	sec-but	H	H	Me	H	H	200	0.6	333.3
MC 817	S	H	H	sec-but	NO_2	H	H	H	H	>200	0.25	>800
MC 897	S	H	H	sec-but	H	NO_2	H	H	H	157	0.40	392
MC 863	S	H	H	sec-but	H	H	NO_2	H	H	151	1.5	101
MC 854	S	H	H	sec-but	Cl	H	H	H	H	200	1	200
MC 857	S	H	H	sec-but	H	Cl	H	H	H	116	2	58
MC 859	S	H	H	sec-but	H	H	Cl	H	H	120	5	24
MC 880	S	H	H	sec-but	F	H	H	H	H	200	0.26	769
MC 884	S	H	H	sec-but	H	F	H	H	H	>200	0.7	>286
MC 889	S	H	H	sec-but	H	H	F	H	H	>200	8.7	23
MC 825	S	H	H	sec-but	NH_2	H	H	H	H	>200	21.2	>9
MC 960	S	H	H	sec-but	H	H	NH_2	H	H	>200	23	>8

Table 2. Cytotoxicity and anti-HIV-1 Activity of MC Compounds (continued)

Compd.	X	Y	Z	R	R^1	R^2	R^3	R^4	R^5	[μM] CC_{50} [b]	[μM] EC_{50} [c]	SI [d]
MC 868	S	H	H	sec-but	CF_3	H	H	H	H	>200	32	6.2
MC 959	S	H	H	sec-but	H	H	CF_3	H	H	200	25	8
MC 952	S	H	H	sec-but	OMe	H	H	H	H	>200	1.96	>208
MC 957	S	H	H	sec-but	H	OMe	H	H	H	>200	1.2	>166
MC 964	S	H	H	sec-but	H	H	OMe	H	H	147	14	10.5
MC 1041	S	H	H	sec-but	H	F	H	F	H	>200	1.4	>143
MC 1042	S	H	H	sec-but	H	Me	H	Me	H	133	0.6	222
MC 877	S	H	H	Me	Cl	H	H	H	Cl	>200	3.2	>62
MC 878	S	H	H	iso-prop	Cl	H	H	H	Cl	>200	1.9	>105
MC 886	S	H	H	n-but	Cl	H	H	H	Cl	>200	0.44	>454
MC 885	S	H	H	iso-but	Cl	H	H	H	Cl	>200	0.45	>444
MC 815	S	H	H	sec-but	Cl	H	H	H	Cl	>200	0.14	>1,428
MC 888	S	H	H	c-pent	Cl	H	H	H	Cl	>200	0.4	>500
MC 891	S	H	H	c-hex	Cl	H	H	H	Cl	>200	0.6	>333
MC 871	S	H	H	Me	F	H	H	H	F	200	0.81	247
MC 860	S	H	H	iso-prop	F	H	H	H	F	>200	0.2	>1,000
MC 872	S	H	H	n-but	F	H	H	H	F	162	0.18	900
MC 866	S	H	H	iso-but	F	H	H	H	F	182	0.14	1,300
MC 848	S	H	H	sec-but	F	H	H	H	F	200	0.04	5,000
MC 867	S	H	H	c-pent	F	H	H	H	F	>200	0.08	>2,500
MC 870	S	H	H	c-hex	F	H	H	H	F	200	0.08	2,500
MC 1001	S	H	Me	iso-prop	Cl	H	H	H	Cl	117	1.2	97.5
MC 996	S	H	Me	c-pent	Cl	H	H	H	Cl	78.3	1.0	78.3
MC 1016	S	H	Me	c-hex	Cl	H	H	H	Cl	>200	2.9	>69
MC 1000	S	H	Et	iso-prop	Cl	H	H	H	Cl	>200	0.4	>500
MC 1002	S	H	Et	c-pent	Cl	H	H	H	Cl	23.4	1.0	23.4
MC 1003	S	H	Et	c-hex	Cl	H	H	H	Cl	>200	3.6	>55.5
MC 1007	S	H	Me	iso-prop	F	H	H	H	F	167	0.05	3,340
MC 1044	S	H	Me	iso-but	F	H	H	H	F	>200	0.05	>4,000
MC 1045	S	H	Me	n-but	F	H	H	H	F	>200	0.07	2,857
MC 1110	S	H	Me	sec-but	F	H	H	H	F	>200	0.03	>6,666
MC 1008	S	H	Me	c-pent	F	H	H	H	F	>200	0.03	>6,666
MC 1013	S	H	Me	c-hex	F	H	H	H	F	>200	0.16	>1,250
MC 1005	S	H	Et	iso-prop	F	H	H	H	F	70	0.08	875
MC 1006	S	H	Et	c-pent	F	H	H	H	F	200	0.15	1,333

Table 2. Cytotoxicity and anti-HIV-1 Activity of MC Compounds (continued)

Compd	X	Y	Z	R	R^1	R^2	R^3	R^4	R^5	[μM] CC_{50}[b]	[μM] EC_{50}[c]	SI[d]
MC 1014	S	H	Et	c-hex	F	H	H	H	F	130	0.05	2,600
MC 971	S	H	Me	iso-prop	CH=CH-CH=CH		H	H	H	119	1.1	108
MC 972	S	H	Me	c-pent	CH=CH-CH=CH		H	H	H	93	0.5	186
MC 974	S	H	Me	c-hex	CH=CH-CH=CH		H	H	H	45	0.14	321.4
MC 969	S	H	Et	iso-prop	CH=CH-CH=CH		H	H	H	50	1.5	33.3
MC 973	S	H	Et	c-pent	CH=CH-CH=CH		H	H	H	51	3.0	17
MC 975	S	H	Et	c-hex	CH=CH-CH=CH		H	H	H	16.9	0.18	94
MC 844	S	Me	H	sec-but	Me	H	H	H	H	>200	1.7	>118
MC 845	S	Me	H	sec-but	H	H	Me	H	H	26	0.8	32
MC 925	S	Me	H	sec-but	H	NO_2	H	H	H	>200	0.35	>571
MC 924	S	Me	H	sec-but	H	H	NO_2	H	H	>200	2	>100
MC 909	S	Me	H	sec-but	Cl	H	H	H	H	>200	0.27	>741
MC 910	S	Me	H	sec-but	H	Cl	H	H	H	>200	0.96	>208
MC 911	S	Me	H	sec-but	H	H	Cl	H	H	>200	9.5	20
MC 913	S	Me	H	sec-but	F	H	H	H	H	140	0.41	341
MC 918	S	Me	H	sec-but	H	F	H	H	H	>200	1.2	>166
MC 919	S	Me	H	sec-but	H	H	F	H	H	105	11	9.5
MC 912	S	Me	H	Me	Cl	H	H	H	Cl	>200	3.2	>62
MC 914	S	Me	H	iso-prop	Cl	H	H	H	Cl	>200	1.3	>154
MC 920	S	Me	H	n-but	Cl	H	H	H	Cl	>200	1.17	>171
MC 916	S	Me	H	iso-but	Cl	H	H	H	Cl	>200	1.2	>166
MC 850	S	Me	H	sec-but	Cl	H	H	H	Cl	>200	0.05	>4,000
MC 915	S	Me	H	c-pent	Cl	H	H	H	Cl	>200	1.8	>111
MC 917	S	Me	H	c-hex	Cl	H	H	H	Cl	>200	22	>9
MC 869	S	Me	H	Me	F	H	H	H	F	200	0.19	1,053
MC 881	S	Me	H	iso-prop	F	H	H	H	F	>200	0.05	>4,000
MC 905	S	Me	H	n-but	F	H	H	H	F	>200	0.08	>2,500
MC 921	S	Me	H	iso-but	F	H	H	H	F	64	0.1	640
MC 849	S	Me	H	sec-but	F	H	H	H	F	80	0.001	8,000
MC 922	S	Me	H	c-pent	F	H	H	H	F	>200	0.08	>2,500
MC 923	S	Me	H	c-hex	F	H	H	H	F	>200	0.09	>2,222
MC 1060	S	Me	Me	Me	F	H	H	H	F	>200	0.04	>5,000
MC 1109	S	Me	Me	sec-but	F	H	H	H	F	200	0.03	6,666
MC 1047	S	Me	Me	c-pent	F	H	H	H	F	>200	0.009	>22,222
MC 798	S	Et	H	sec-but	H	H	H	H	H	>200	1.0	>200

Table 2. Cytotoxicity and anti-HIV-1 Activity of MC Compounds (continued)

Compd.	X	Y	Z	R	R^1	R^2	R^3	R^4	R^5	[μM] CC_{50} [b]	[μM] EC_{50} [c]	SI [d]
MC 1037	S	Et	H	iso-prop	F	H	H	H	F	65	0.2	326
MC 1038	S	Et	H	sec-but	F	H	H	H	F	>200	0.1	>2,000
MC 804	S	Et	H	sec-but	CH=CH-CH=CH		H	H	H	>200	5.3	>34
MC 1039	S	iso-prop	H	iso-prop	F	H	H	H	F	>200	0.4	>500
MC 852	S	allyl	H	sec-but	H	H	H	H	H	>200	3	>67
MC 856	S	n-prop	H	sec-but	H	H	H	H	H	190	12	16
MC 834	S	n-but	H	sec-but	H	H	H	H	H	>200	>200	-
MC 1119	NH	H	H	ethyl	F	H	H	H	F	>200	0.8	>250
MC 1078	NH	H	H	n-prop	F	H	H	H	F	200	0.11	1,818
MC 979	NH	H	H	iso-prop	F	H	H	H	F	>200	0.38	>526
MC 980	NH	H	H	c-prop	F	H	H	H	F	>200	3.17	>63
MC 1077	NH	H	H	n-but	F	H	H	H	F	100	0.10	1,000
MC 945	NH	H	H	sec-but	F	H	H	H	F	>200	0.13	>1,540
MC 1043	NH	H	H	MeOethyl	F	H	H	H	F	>200	0.8	>250
MC 1022	NH	H	H	c-pent	F	H	H	H	F	>200	0.09	>2,222
MC 1049	NH	H	H	c-hex	F	H	H	H	F	66	0.14	471
MC 1048	NH	H	Me	c-pent	F	H	H	H	F	75	0.03	2,500
MC 1118	NH	Me	H	iso-prop	F	H	H	H	F	190	0.03	6,333
MC 1130	NH	Me	H	sec-but	F	H	H	H	F	200	0.07	2,857
MC 1050	NH	Me	H	c-pent	F	H	H	H	F	>200	0.02	>10,000
MC 1105	NH	Me	H	benzyl	F	H	H	H	F	50	0.50	100
MC 1129	NH	Me	H	c-pent	F	H	H	H	F	90	0.02	4,500
MC 1167	NH	H	H	Me	F	H	H	H	F	>200	1.5	>133
MC 1168	NH	Me	H	Me	F	H	H	H	F	135	0.4	335
MC 1186	NH	Me	H	n-prop	F	H	H	H	F	>200	0.02	>10,000
MC 1185	NH	Me	H	n-but	F	H	H	H	F	>200	0.02	>10,000
MC 1178	NH	H	Me	Me	F	H	H	H	F	106	0.11	964
MC 1190	NH	H	Me	n-prop	F	H	H	H	F	103	0.02	5,150
MC 1191	NH	H	Me	iso-prop	F	H	H	H	F	115	0.03	3,830
MC 1189	NH	H	Me	n-but	F	H	H	H	F	52	0.03	1,730
MC 1192	NH	H	Me	sec-but	F	H	H	H	F	86	0.04	2,150
MC 1180	NH	H	Me	c-hex	F	H	H	H	F	56	0.02	2,545
MC 1170	NH	Me	Me	Me	F	H	H	H	F	200	0.03	>6,666
MC 1187	NH	Me	Me	n-but	F	H	H	H	F	83	0.01	8,300
MC 1181	NH	Me	Me	c-hex	F	H	H	H	F	58	0.03	2,231

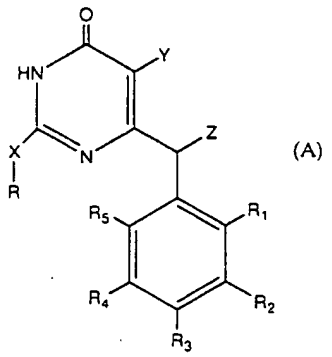
Table 2. Cytotoxicity and anti-HIV-1 Activity of MC Compounds (continued)

Compd.	X	Y	Z	R	R^1	R^2	R^3	R^4	R^5	[μM] CC_{50} [b]	[μM] EC_{50} [c]	SI [d]
MC 1182	N	H	H	Me_2	F	H	H	H	F	>200	0.05	>4,000
MC 1183	N	H	H	Me-piperaz	F	H	H	H	F	>200	7.1	>28
MC 1188	N	H	H	morph	F	H	H	H	F	>200	0.6	>333
MC 1193	N	H	H	thiomorph	F	H	H	H	F	>200	0.05	>4,000
MC 1194	N	H	H	piperid	F	H	H	H	F	>200	0.02	>10,000
MC 1196	N	H	H	pyrrolid	F	H	H	H	F	>200	2.1	>95
MC 1202	N	H	H	Et_2	F	H	H	H	F	>200	0.26	>769
MC 1204	N	H	H	$(n\text{-prop})_2$	F	H	H	H	F	>200	3.8	>53
MC 1195	N	Me	H	Me_2	F	H	H	H	F	>200	0.02	>10,000
MC 1203	N	Me	H	Me-piperaz	F	H	H	H	F	>200	0.36	>555
MC 1205	N	Me	H	morph	F	H	H	H	F	>200	0.047	>4,255
MC 1206	N	Me	H	thiomorph	F	H	H	H	F	>200	0.09	>2,222
MC 1137	S	Me	Me	iso-prop	F	H	H	H	F	200	0.007	28,571
MC 1175	S	Me	Me	n-but	F	H	H	H	F	112	0.008	14,000
MC 1153	S	Me	Me	iso-but	F	H	H	H	F	>200	0.01	>20,000
MC 1174	S	Me	Me	c-hex	F	H	H	H	F	>200	0.018	>11,111
MC 1047+	S	Me	Me	c-pent	F	H	H	H	F	>200	0.002	>100,000
MC 1047-	S	Me	Me	c-pent	F	H	H	H	F	>200	0.7	>286
MC 1161	S	H	H	MeSMe	F	H	H	H	F	>200	0.80	>250
MC 1162	S	Me	H	MeSMe	F	H	H	H	F	30	0.12	250
MC 1157	S	Et	H	MeSMe	F	H	H	H	F	50	0.11	454
MC 1145	S	iso-prop	H	MeSMe	F	H	H	H	F	200	0.10	2,000
MC 1140	S	H	H	MeSMe	H	H	H	H	H	>200	20	>10

[a] Data represent mean values of at least two separate experiments. [b] Compound dose required to reduce the viability of mock-infected cells by 50%, as determined by the MMT method. [c] Compound dose required to achieve 50% protection of MT-4 cells from HIV-1 induced cytopathogenicity, as determined by the MTT method. [d] Selectivity index, CC_{50}/EC_{50} ratio.

WHAT IS CLAIMED IS:

1. A compound of the formula:



(A)

wherein:

X is -0, $-CH_2$, -CHK (wherein K is -H, $-C_{1-4}$alkyl, $-C_{3-6}$cycloalkyl), -S, -NK (wherein K is -H, $-C_{1-4}$alkyl, $-C_{3-6}$cycloalkyl), -aryl, -arylalkyl;

R is -H, $-C_{1-4}$alkyl (containing one or more of heteroatoms like O, S, N), $-C_{3-6}$cycloalkyl (containing one or more of heteroatoms like O, S, N), -aryl, arylalkyl, heterocycle;

Y is -H, $-C_{1-4}$alkyl, $-C_{3-6}$cycloalkyl;

Z is -H, $-C_{1-4}$alkyl, $-C_{3-6}$cycloalkyl;

R_1 is $-H_1$ $-C_{1-4}$alkyl, halogen, $-NO_2$, -OW (wherein W is -H, $-CH_3$, -aryl), -SW (wherein W is -H, $-CH_3$, -aryl);

R_2 is -H, $-C_{1-4}$alkyl, -halogen, $-NO_2$, -OW (wherein W is -H, $-CH_3$, -aryl), -SW (wherein W is -H, $-CH_3$, -aryl);

R_3 is -H, $-C_{1-4}$alkyl, -halogen, $-NO_2$, -OW (wherein W is -H, $-CH_3$, aryl), -SW (wherein W is -H, $-CH_3$, -aryl);

R_4 is -H, $-C_{1-4}$alkyl, -halogen, $-NO_2$, -OW (wherein W is -H, $-CH_3$, -aryl), -SW (wherein W is -H, $-CH_3$, -aryl);

R_5 is -H, $-C_{1-4}$alkyl, -halogen, $-NO_2$, -OW (wherein W is -H, $-CH_3$, -aryl), -SW (wherein W is -H, $-CH_3$, -aryl), or a pharmaceutically acceptable salt or soluble derivative thereof.

2. A compound having formula A as claimed in claim 1 wherein

X = O Y = H Z = H R = *s*Bu R_1 = F R_2 = H R_3 = H R_4 = H R_5= F

X = O Y = H Z = H R = *c*Pen R_1 = F R_2 = H R_3 = H R_4 = H R_5=F.

3. A compound having formula A as claimed in claim 1 wherein

X = S Y = H Z = H R = *s*Bu R_1 = NO_2 R_2 = H R_3 = H R_4 = H R_5=H

X = S Y = H Z = H R = *s*Bu R_1 = F R_2 = H R_3 = H R_4 = H R_5=H

X = S Y = H Z = H R = CH_3 R_1 = Cl R_2 = H R_3 = H R_4 = H R_5=Cl

X = S Y = H Z = H R = *i*pr R_1 = Cl R_2 = H R_3 = H R_4 = H R_5 = Cl

X = S Y = H Z = H R = *n*Bu R_1 = Cl R_2 = H R_3 = H R_4 = H R_5 = Cl

X = S Y = H Z = H R = *i*Bu R_1 = Cl R_2 = H R_3 = H R_4 = H R_5 = Cl

X = S Y = H Z = H R = *s*Bu R_1 = Cl R_2 = H R_3 = H R_4 = H R_5 = Cl

X = S Y = H Z = H R = *c*Pen R_1 = Cl R_2 = H R_3 = H R_4 = H R_5 = Cl

X = S Y = H Z = H R = *c*Es R_1 = Cl R_2 = H R_3 = H R_4 = H R_5 = Cl

X = S Y = H Z = H R = CH_3 R_1 = F R_2 = H R_3 = H R_4 = H R_5 = F

X = S Y = H Z = H R = *i*Pr R_1 = F R_2 = H R_3 = H R_4 = H R_5 = F

X = S Y = H Z = H R = *n*Bu R_1 = F R_2 = H R_3 = H R_4 = H R_5 = F

X = S Y = H Z = H R = *i*Bu R_1 = F R_2 = H R_3 = H R_4 = H R_5 = F

X = S Y = H Z = H R = *s*Bu R_1 = F R_2 = H R_3 = H R_4 = H R_5 = F

X = S Y = H Z = H R = *c*Pen R_1 = F R_2 = H R_3 = H R_4 = H R_5 = F

X = S Y = H Z = H R = *c*Es R_1 = F R_2 = H R_3 = H R_4 = H R_5 = F

X = S Y = H Z = CH_3 R = *i*Pr R_1 = Cl R_2 = H R_3 = H R_4 = H R_5 = Cl

X = S Y = H Z = CH_3 R = *c*Pen R_1 = Cl R_2 = H R_3 = H R_4 = H R_5 = Cl

X = S Y = H Z = CH_3 R = *c*Es R_1 = Cl R_2 = H R_3 = H R_4 = H R_5 = Cl

X = S Y = H Z = Et R = *i*Pr R_1 = Cl R_2 = H R_3 = H R_4 = H R_5 = Cl

X = S Y = H Z = Et R = *c*Pen R_1 = Cl R_2 = H R_3 = H R_4 = H R_5 = Cl

X = S Y = H Z = Et R = *c*Es R_1 = Cl R_2 = H R_3 = H R_4 = H R_5 = Cl

X = S Y = H Z = CH_3 R = *i*Pr R_1 = F R_2 = H R_3 = H R_4 = H R_5 = F

X = S Y = H Z = CH_3 R = *i*Bu R_1 = F R_2 = H R_3 = H R_4 = H R_5 = F

X = S Y = H Z = CH_3 R = *n*Bu R_1 = F R_2 = H R_3 = H R_4 = H R_5 = F

X = S Y = H Z = CH_3 R = *s*Bu R_1 = F R_2 = H R_3 = H R_4 = H R_5 = F

X = S Y = H Z = CH_3 R = *c*Pen R_1 = F R_2 = H R_3 = H R_4 = H R_5 = F

X = S Y = H Z = CH_3 R = *c*Es R_1 = F R_2 = H R_3 = H R_4 = H R_5 = F

X = S Y = H Z = Et R = *i*Pr R_1 = F R_2 = H R_3 = H R_4 = H R_5 = F

X = S Y = H Z = Et R = *c*Pen R_1 = F R_2 = H R_3 = H R_4 = H R_5 = F

X = S Y = H Z = Et R = *c*Es R_1 = F R_2 = H R_3 = H R_4 = H R_5 = F

X=S Y = H Z=CH_3 R= *c*Es -CH=CH-CH=CH R_3=H R_4=H R_5=H

X = S Y = H Z = H R = *s*Bu R_1 = Cl R_2 = H R_3 = H R_4 = H R_5 = H

X = S	Y = CH_3	Z = H	R = *s*Bu	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = H	
X = S	Y = CH_3	Z = H	R = *s*Bu	R_1 = Cl	R_2 = H	R_3 = H	R_4 = H	R_5 = Cl	
X = S	Y = CH_3	Z = H	R = CH_3	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = CH_3	Z = H	R = *i*Pr	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = CH_3	Z = H	R = *n*Bu	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = CH_3	Z = H	R = *i*Bu	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = CH_3	Z = H	R = *s*Bu	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = CH_3	Z = H	R = *c*Pen	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = CH_3	Z = H	R = *c*Es	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = CH_3	Z = CH_3	R = CH_3	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = CH_3	Z = CH_3	R = *s*Bu	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = CH_3	Z = CH_3	R = *c*Pe	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = Et	Z = H	R = *s*Bu	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = *i*Pr	Z = H	R = *i*Pr	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = CH_3	Z = CH_3	R = *i*Pr	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = CH_3	Z = CH_3	R = *n*Bu	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = CH_3	Z = CH_3	R = *i*Bu	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = CH_3	Z = CH_3	R = *c*Es	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = H	Z = H	R=MeSMe	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = CH_3	Z = H	R=MeSMe	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = Et	Z = H	R=MeSMe	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = S	Y = *i*Pr	Z = H	R=MeSMe	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F.	

4. A compound having formula A as claimed in claim 1 wherein

X = NH	Y = H	Z = H	R = Et	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = NH	Y = H	Z = H	R = *n*Pr	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = NH	Y = H	Z = H	R = *i*Pr	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = NH	Y = H	Z = H	R = *c*Pr	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = NH	Y = H	Z = H	R = *n*Bu	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = NH	Y = H	Z = H	R = *s*Bu	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = NH	Y = H	Z = H	R=MeOEt	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = NH	Y = H	Z = H	R = *c*Pe	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = NH	Y = H	Z = H	R = *c*Es	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = NH	Y = H	Z = CH_3	R = *c*Pe	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = NH	Y = CH_3	Z = H	R = *i*Pr	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = NH	Y = CH_3	Z = H	R = *s*Bu	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = NH	Y = CH_3	Z = H	R = *c*Pe	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	
X = NH	Y = CH_3	Z = H	R = benz	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F	

X = NH	Y = CH_3	Z = CH_3	R = *c*Pe	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = NH	Y = H	Z = H	R = CH_3	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = NH	Y = CH_3	Z = H	R = CH_3	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = NH	Y = CH_3	Z = H	R = *n*Pr	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = NH	Y = CH_3	Z = H	R = *n*Bu	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = NH	Y = H	Z = CH_3	R = CH_3	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = NH	Y = H	Z = CH_3	R = *n*Pr	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = NH	Y = H	Z = CH_3	R = *i*Pr	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = NH	Y = H	Z = CH_3	R = *n*Bu	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = NH	Y = H	Z = CH_3	R = *s*Bu	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = NH	Y = H	Z = CH_3	R = *c*Es	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = NH	Y = CH_3	Z = CH_3	R = CH_3	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = NH	Y = CH_3	Z = CH_3	R = *n*Bu	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = NH	Y = CH_3	Z = CH_3	R = *c*Es	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = N	Y = H	Z = H	R=$(CH_3)_2$	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = N	Y = H	Z = H	R=Me-Pip	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = N	Y = H	Z = H	R= Morph	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = N	Y = H	Z = H	R=S-morp	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = N	Y = H	Z = H	R= Piper	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = N	Y = H	Z = H	R=Pyrroli	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = N	Y = H	Z = H	R = Et_2	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = N	Y = H	Z = H	R=$(n\text{Pr})_2$	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = N	Y = CH_3	Z = H	R=$(CH_3)_2$	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = N	Y = CH_3	Z = H	R=Me-Pip	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = N	Y = CH_3	Z = H	R= Morph	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F
X = N	Y = CH_3	Z = H	R=S-morp	R_1 = F	R_2 = H	R_3 = H	R_4 = H	R_5 = F.

5. A pharmaceutically acceptable salt or soluble derivative of a compound of claim 1.

6. A process for the preparation of a compound having formula A as claimed in claim 1 wherein X = 0, wherein the proper methyl arylacetylalkylacetate is reacted with O-methylisourea in presence of calcium hydroxide; the so obtained 2-O-methyl(5-alkyl)-6-benzyl(substituted)uracils are reacted with the proper potassium alkoxide according to scheme A.

7. A process for the preparation of a compound having formula A as claimed in claim 1 wherein X = S, wherein the proper ethyl arylacetylalkylacetate is reacted with thiourea in presence of sodium methoxide; the so obtained 5-alkyl-6-benzyl(substituted)-2-

thiouracils are reacted with methyl iodide or with an alkyl halide in a basic medium according to scheme B.

8. A process for the preparation of the compounds having formula A as claimed in claim 1 wherein X = NK (wherein K is -H, -C_{1-4}alkyl, -C_{3-6}cycloalkyl), wherein the proper S-methyl(5-alkyl)-6-benzyl(substituted)-2-thiouracil is reacted with the proper amine according to scheme C.

9. A method of preventing infection of HIV, or of treating infection by HIV or of treating AIDS, comprising administering to a mammal an effective amount of a compound as claimed in claim 1 or a pharmaceutically acceptable salt or soluble derivative thereof.

10. A pharmaceutical composition useful for inhibiting HIV reverse transcriptase, comprising an effective amount of a compound claimed in claim 1 or a pharmaceutically acceptable salt or soluble derivative thereof, and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition useful for preventing or treating infection of HIV or for treating AIDS, comprising an effective amount of a compound as claimed in claim 1 or a pharmaceutically acceptable salt or soluble derivative thereof, and a pharmaceutically acceptable carrier.

12. A method of preventing infection of HIV, or of treating infection by HIV or of treating AIDS, comprising administering to a mammal an effective amount of a compound as claimed in claim 1 or a pharmaceutically acceptable salt or soluble derivative thereof in combination with another anti-HIV agent selected from the group consisting of abacavir, zidovudine, BILA 1906, BILA 2185, BM+51.0836: triazoloisoindolinone derivative, BMS 186,318: aminodiol derivative HIV-1 protease inhibitor, d4API, stavudine, efavirenz, HBY097, HEPT, KNI-272, L-697,593, L-735,524, L-697,661, L-FDDC, L-FDOC, nevirapine, foscarnet, PMEA, PMPA, Ro 31-8959, RPI-3121, SC-52151, SC-55389A, TIBO R82150, TIBO 82913, TSAO-m3T, U90152, UC: thiocarboxanilide derivatives, UC-781, UC-82, VB 11,328, amprenavir, XM 323, delaviridine, famciclovir, gancyclovir, penciclovir, indinavir, nelfinavir, ritonavir, saquinavir, DDI, DDC, Delaviridine, β-LddA, β-L-3'-azido-d5FC, carbovir, acyclovir, interferon, stavudine, (3'-azido-2',3'-dideoxy-5-methyl-cytidine), 3'-azido nucleosides, β-D-dioxolane nucleosides such as β-D-dioxolanylguanine (DXG), β-D-dioxolanyl-2,6-diaminopurine (DAPD), and β-D-dioxolanyl-6-chloropurine (ACP), D4T, FTC, 3TC, AZDU, and amprenavir.

INTERNATIONAL SEARCH REPORT

In rtional Application No
PCT/EP 99/05134

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/52 C07D239/56 C07D239/46 C07D239/36 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANTONELLO MAI ET AL.: "SYNTHESIS AND ANTI-HIV-1 ACTIVITY OF THIO ANALOGUES OF DIHYDROALKOXYBENZYLOXYPYRIMIDINES" JOURNAL OF MEDICINAL CHEMISTRY., vol. 38, no. 17, 18 August 1995 (1995-08-18), pages 3258-63, XP000578131 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 page 3258 -page 3262	1,5,6, 10,11

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 November 1999	03/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/EP 99/05134

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 122, no. 1, 1995 Columbus, Ohio, US; abstract no. 122513c, S. MASSA,A. MAI: "SYNTHESIS AND ANTIVIRAL ACTIVITY OF NEW 3,4-DIHYDRO-2-ALKOXY-6-BENZYL-4-OXOPYRIMIDINES" page 23; XP002123508 abstract & ANTIVIRAL CHEM. CHEMOTHER., vol. 6, no. 1, 1995, pages 1-8, ENG	1,5,6, 10,11
X	WO 91 18887 A (SMITH-KLINE) 12 December 1991 (1991-12-12) page 24; claims	1,5
X	CHEMICAL ABSTRACTS, vol. 88, no. 21, 1978 Columbus, Ohio, US; abstract no. 152555q, H. FENNER ET AL.: "PYRIMIDO(5,4-B)QUINOLINES" page 604; XP002123509 abstract & ARCH. PHARM., vol. 311, no. 2, 1978, pages 115-125, WEINHEIM	1
P,X	ANTONELLO MAI ET AL.: "5-ALKYL-2-ALKYLTHIO-6-(2,6-DIHALOPHENYLMETHYL)-3,4-DIHYDROPYRIMIDIN-4(3H)-ONES" JOURNAL OF MEDICINAL CHEMISTRY., vol. 42, no. 4, 25 February 1999 (1999-02-25), pages 619-627, XP002123507 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 page 619 -page 626	1,3,5-7, 10,11

1

INTERNATIONAL SEARCH REPORT

...ernational application No.
PCT/EP 99/05134

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ·tional Application No
PCT/EP 99/05134

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9118887 A	12-12-1991	AU 7971691 A	31-12-1991